Case Report

Recurrence of Proliferative Glomerulonephritis with Monoclonal IgG Deposits with a Striated Ultrastructure

Tomoko Namba-Hamano[a], Takayuki Hamano[a,b], Ryoichi Imamura[c], Yutaka Yamaguchi[d], Masahiro Kyo[e], Hiroaki Yonishi[a], Atsushi Takahashi[a], Masataka Kawamura[c], Shigeaki Nakazawa[c], Taigo Kato[c], Toyofumi Abe[c], Miyaji Kyakuno[f], Yoshitsugu Takabatake[a], Norio Nonomura[c], Yoshitaka Isaka[a]

[a]Department of Nephrology, Osaka University Graduate School of Medicine, Osaka, Japan

[b]Department of Nephrology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

[c]Department of Urology, Osaka University Graduate School of Medicine, Osaka, Japan

[d]Yamaguchi's Pathological Laboratory, Chiba, Japan

[e]Osaka Umeda Iseikai Daialysis Clinic, Osaka, Japan

[f]Department of Kidney Transplantation, Takatsuki General Hospital, Osaka, Japan

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Corresponding author

Tomoko Namba-Hamano

Department of Nephrology

Osaka University Graduate School of Medicine

2-2, Yamada-oka,

Suita, Osaka, 565-0871, Japan

Tel: +81-6-6879-3857

E-mail: namba@kid.med.osaka-u.ac.jp

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Abstract

A 64-year-old man with nephrotic syndrome was admitted to another hospital where his renal biopsy revealed membranoproliferative glomerulonephritis (MPGN) with monoclonal immunoglobulin (Ig) G, subclass 1, κ light chain (IgG1κ) deposition on immunofluorescence (IF). Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) was suspected due to monoclonal IgG1κ deposits and the absence of hematological abnormalities. However, the typical PGNMID phenotype was not observed by electron microscopy. Instead, an organized and striated muscle-like structure was observed in the subendothelial space. Since a 2-year treatment with immunosuppressants did not improve his proteinuria, a second biopsy was performed at our hospital. It showed an MPGN-like phenotype; however, monoclonal immunoglobulin deposits on IF were no longer observed. One year after the second biopsy, he developed end-stage renal disease. Thus, he underwent living kidney transplantation from his wife. Allograft biopsy was performed as proteinuria was observed 3 months after transplantation, which again showed an MPGN-like phenotype with monoclonal IgG1κ deposits. The observed electron-dense deposits were similar to those in the native biopsies. Accordingly, the patient was diagnosed with recurrent MPGN. Adding methylprednisolone pulse therapy to conventional immunosuppressants did not improve the

patient's renal function or proteinuria. He died of Legionella pneumonia 8 months after transplantation. Considering the patient's histological findings of MPGN with monoclonal IgG1κ deposits and early recurrence of glomerulonephritis after transplantation, he was diagnosed with PGNMID with novel electron-dense deposits.

Introduction

Recurrent glomerulonephritis has attracted attention as a cause of graft loss after kidney transplantation in recent advancements in immunosuppressive treatment [1,2]. Membranoproliferative glomerulonephritis (MPGN) with monoclonal immunoglobulin deposits shows a higher recurrence rate after transplantation than MPGN with polyclonal immunoglobulin, with subsequent progression to graft loss [3].

Proliferative glomerulonephritis with monoclonal immunoglobulin G (IgG) deposits (PGNMID), described by Nasr et al. [4], is characterized by MPGN-like histological findings and glomerular deposition of monoclonal immunoglobulin. However, only 10%–30% patients with PGNMID have M protein [5,6]. A recent study revealed that PGNMID frequently recurs early after transplantation.

We present a case of recurrent PGNMID with a novel and unclassified organized glomerular structure.

Case Report

Clinical course of a native kidney

A 64-year-old Japanese man was hospitalized with lower leg edema. Although proteinuria had been noted 3 years before admission, he had not received treatment. No remarkable family history was noted. Upon admission, the patient's blood pressure was 179/119 mmHg; urinalysis showed proteinuria of 9.4 g/g Creatinine (Cr) and hematuria (2+). Laboratory examination revealed the following: serum Cr, 1.45 mg/dL; total protein, 4.1 g/dL; albumin, 1.7 g/dL; low-density lipoprotein, 208 mg/dL; and IgG, 627 mg/dL. Serum complement levels were within the normal ranges. Light microscopy of the first renal biopsy specimen revealed lobular glomerular alterations with mesangial and endocapillary hypercellularity and glomerular basement membrane duplication, typical of MPGN. Immunofluorescence (IF) revealed weak glomerular staining for IgG, IgM, C3, C1q,

and fibrinogen, with a peripheral capillary pattern. Subsequent immunostaining for IgG subclasses and light chains revealed monoclonal IgG1κ deposition with a similar peripheral pattern. Despite monoclonal IgG1κ deposition in the glomeruli, M protein was not detected in the blood or urine, and there was no evidence of plasma cell dysplasia. Electron microscopy revealed the accumulation of organized deposits with a striated pattern in the subendothelial space and mesangial area, atypical for MPGN. These electron-dense bands were 10–12-nm wide with a 25–30-nm distance of periodicity. Markers of secondary MPGN, including antinuclear antibody, cryoglobulin, and antibodies for hepatitis B and C, were not detected. The patient was diagnosed with primary MPGN, and oral prednisolone (35 mg/day) was administered. Considering that 1-year immunosuppressive treatment was not effective in improving the patient's proteinuria and renal dysfunction, he was referred to our hospital, and a second biopsy was performed 2 years after the first biopsy.

Findings on the second biopsy were similar to those of the first biopsy, except for IF results; different from the first biopsy, no significant staining for immunoglobulin or complement was observed. The second biopsy specimen included a higher percentage of sclerotic glomeruli (27%) than the first biopsy specimen (15%). Moreover, the glomeruli of the second biopsy specimen on IF were more sclerotic compared to those of the first biopsy specimen, and the deposition could not be detected. This probably explains the discrepancy in terms of monoclonal deposition between the first and second biopsies. There was no evidence of a hematological disorder or secondary MPGN. Subsequent 1-year immunosuppressive treatment did not improve patient's renal function, and hemodialysis was initiated.

Clinical course of the allograft kidney

Two years later, at the age of 68, he underwent ABO-incompatible living kidney transplantation (blood type A to O) from his 68-year-old wife. For preoperative desensitization, rituximab (200 mg/body) was administered 2 weeks before transplantation, and 2 sessions of plasmapheresis

followed by plasma exchange (PE) were performed. Baseline allograft biopsy showed no significant abnormality except for mild arteriosclerosis. A maintenance immunosuppressive regimen included prednisolone, tacrolimus (TAC), and mycophenolate mofetil (MMF). Serum Cr increased from 1.29 mg/dL to 2.37 mg/dL 3 weeks after transplantation. The second allograft biopsy, which was performed 3 weeks after transplantation, showed endocapillary proliferation and peritubular capillaritis without mesangial proliferation. Although we found positive staining for C4d on the peritubular capillaries on immunohistochemistry, these results might be attributed to ABO-incompatible kidney transplantation. Considering the absence of positive staining for immunoglobulin and complements on IF, these findings were consistent with active antibody-mediated rejection. Methylprednisolone pulse therapy and rituximab were included in the maintenance therapy, followed by 2 sessions of PE and 6 g of intravenous immunoglobulin. The additional treatment restored serum Cr to 1.51 mg/dL and the patient was discharged. Two months after discharge, his proteinuria protein level increased to 6.8 g/gCr with a slight increase in serum Cr level to 1.75 mg/dL. Hence, we performed a third allograft biopsy 3 months after transplantation. Light microscopy revealed the absence of sclerotic glomeruli; however, more than half of the 23 glomeruli showed mesangial proliferation with nodules, which were negative for Congo red staining. Endocapillary proliferation and cellular crescents were also observed in some glomeruli, with segmental glomerular basement membrane duplication (Fig. 1). Mild interstitial fibrosis, tubular atrophy, and intimal fibroelastosis were observed, with no evidence of rejection. No immunoglobulin or complement was detected on IF-stained frozen tissues. Immunohistochemistry of paraffin-embedded tissues digested with proteinase revealed monoclonal IgGκ1 deposits, with peripheral and mesangial patterns (Fig. 2). Electron microscopy revealed a few dense deposits with striated ultrastructure in the subendothelial space and paramesangial area, similar to those observed in the native kidney biopsies (Fig. 3). Accordingly, the patient was diagnosed with recurrent glomerulonephritis. Methylprednisolone pulse therapy

was added to maintenance immunosuppressive therapy for the treatment of proteinuria (4–6 g/gCr) and kidney disease as evidenced by the elevated serum Cr level of 2.38 mg/dL. At 8 months after transplantation, the patient was admitted following the complaints of fever and dyspnea, and he was diagnosed with Legionella pneumonia. Antibiotics were ineffective, and he subsequently died.

Discussion

We report a case of novel MPGN with monoclonal immunoglobulin deposits and recurrence early after transplantation. Proteinuria was observed 1 month after transplantation, and histological recurrence was confirmed with a protocol biopsy performed 3 months later.

Based on the pathological features of MPGN and monoclonal immunoglobulin deposits in the glomeruli, with the absence of M protein, this case met the criteria for PGNMID described by Nasr et al. [4]. Features observed on electron microscopy typical of PGNMID include unorganized granular deposits localized to the subendothelial space, the mesangial area, and/or the subepithelial space. The clinical outcomes are variable, with approximately 25% of patients developing end-stage renal disease refractory to immunosuppressive treatment within 2.5 years [7]. A recent study of protocol biopsies revealed that PGNMID had a high recurrence rate (89%) early after transplantation. In this study, approximately half of the patients lost graft function within 3 years after diagnosis [6]. Kawanishi et al. reported a case of recurrent PGNMID leading to rapid graft loss after transplantation [8]. Considering a high recurrence rate and poor prognosis, careful consideration is required to perform kidney transplantation for patients progressing to end-stage renal disease due to PGNMID.

The presence of monoclonal immunoglobulin deposits in the kidney is highly suggestive of the presence of underlying B-cell or plasma cell clones. Renal diseases with monoclonal immunoglobulin are likely to recur after transplantation due to impaired eradication of small B-cell

clones. PGNMID has a shorter time to recurrence than light chain amyloidosis and monoclonal immunoglobulin deposition disease (MIDD). Despite monoclonal immunoglobulin deposits in the kidney, repeated hematological evaluations failed to detect significant abnormalities. Only 10%–30% patients with PGNMID had detectable M protein in the serum and urine electrophoresis (EP) or immunofixation [5,6]. A possible explanation is that the amount of monoclonal immunoglobulin was significantly small for detection using the serum or urine EP due to a few underlying B-cell clones.

This case showed unusually organized deposits exclusively in the glomeruli on electron microscopy. The deposits contained regularly stacked electron-dense bands in a parallel arrangement, resembling striated myofibrils. Organized patterns of fibrils, microtubules, and granular deposits have typically been observed in renal diseases [9]. The striated structure observed in the present case was different and could not be conventionally classified. Although the present case showed ultrastructure similar to fibrin tactoids, its periodicity (25–30 nm) was slightly longer than that of fibrin tactoids (22–23 nm) [10]. Some studies have reported cases of renal disease with similar ultrastructure [11,12]. The patient's medical story before transplantation in this present case report was summarized in another paper [13]. There was no evidence of systemic disease such as cryoglobulinemia, except for 1 case with multiple myeloma. On light microscopy, all cases showed similar features, with negative Congo red staining results and MPGN-like findings. The IF results varied. Some cases were positive for C3 and C1q, while others showed no positive findings.

The present case showed similar electron-dense deposits with a striated ultrastructure, but 2 unique features were observed. First, this patient relapsed after ABO-incompatible transplantation, suggesting pathology refractory to conventional immunosuppressants including TAC and MMF and to rituximab and PE, although a recent study reported the efficacy of clone-directed therapy that

included rituximab [14]. Second, we found monoclonal deposits using antigen retrieval. Conventional IF was negative for immunoglobulins and complements. However, IgG1κ deposition was unmasked on immunohistochemistry by protease digestion using paraffin-embedded formalin-fixed tissue. Similar false-negative cases were reported in studies showing the usefulness of antigen retrieval [15]. In cases of MPGN negative for immunoglobulin on IF, unmasking by antigen retrieval should be considered.

A case of PGNMID with another atypical organized deposit was reported [16]. The appearance of the deposits in this case was microlamellar, which was different from the striated muscle-like structure observed in the present case. Considering the definition of PGNMID by Nasr et al., cases with unusual deposits can be diagnosed as atypical PGNMID. Further investigation is needed to elucidate the identity of these deposits.

In conclusion, we report a case of recurrent PGNMID with atypical electron-dense deposits. This is the first report of early recurrence of atypical PGNMID with a striated ultrastructure after transplantation. To detect monoclonal immunoglobulin deposits with negative staining on IF, immunohistochemistry of paraffin-embedded tissues digested with proteinase was effective.

Statements

Statement of Ethics

Written informed consent of the patient for publication has been obtained.

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Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

T. N-H and T. H drafted and revised the manuscript. R. I, A.T, M. K, S.N, T. K, T.A, M. K, and Y.T saw the patient directly. Y. Y. and M. K. scrutinized renal biopsy samples. N.N and Y.I provided critical review, advice, and consultation throughout the writing of the manuscript.

References

1. Briganti EM, Russ GR, McNeil JJ, Atkins RC, Chadban SJ. Risk of renal allograft loss from recurrent glomerulonephritis. N Engl J Med. 2002 Jul;347(2):103–9.
2. Floege J. Recurrent glomerulonephritis following renal transplantation: an update. Nephrol Dial Transplant. 2003 Jul;18(7):1260–5.
3. Cosio FG, Cattran DC. Recent advances in our understanding of recurrent primary glomerulonephritis after kidney transplantation. Kidney Int. 2017 Feb;91(2):304–14.
4. Nasr SH, Markowitz GS, Stokes MB, Seshan SV, Valderrama E, Appel GB, et al. Proliferative glomerulonephritis with monoclonal IgG deposits: a distinct entity mimicking immune-complex glomerulonephritis. Kidney Int. 2004 Jan;65(1):85–96.
5. Bridoux F, Leung N, Hutchison CA, Touchard G, Sethi S, Fermand JP, et al. Diagnosis of monoclonal gammopathy of renal significance. Kidney Int. 2015 Apr;87(4):698–711.
6. Said SM, Cosio FG, Valeri AM, Leung N, Sethi S, Salameh H, et al. Proliferative glomerulonephritis with monoclonal immunoglobulin G deposits is associated with high rate of early recurrence in the allograft. Kidney Int. 2018 Jul;94(1):159–69.
7. Nasr SH, Satoskar A, Markowitz GS, Valeri AM, Appel GB, Stokes MB, et al. Proliferative glomerulonephritis with monoclonal IgG deposits. J Am Soc Nephrol. 2009 Sep;20(9):2055–64.
8. Kawanishi K, Honda K, Horita S, Koike J, Shimizu T, Tanabe K, et al. Recurrent proliferative glomerulonephritis with monoclonal immunoglobulin G deposits leads to rapid graft loss after kidney transplantation: a case report. CEN Case Rep. 2014 Nov;3(2):139–44.
9. Herrera GA, Turbat-Herrera EA. Renal diseases with organized deposits: an algorithmic approach to classification and clinicopathologic diagnosis. Arch Pathol Lab Med. 2010 Apr;134(4):512–31.
10. Samy S. Iskandar, Guillermo A. Herrera. Glomerular diseases with organized deposits. In: J. Charles Janette, Jean L. Olson, Fred G. Silva, Vivette D. D'Agati, editors. Heptinstall's pathology of the kidney. Philadelphia: Lippincott Williams & Wilkins (LWW); 2014. Vol. 2; p. 1015–39.
11. Ohtani H, Wakui H, Komatsuda A, Goto H, Tada M, Ozawa M, et al. Progressive glomerulopathy with unusual deposits of striated structures: a new disease entity? Nephrol Dial Transplant. 2010 Jun;25(6):2016–9.
12. Lee Y G, Shin DY, Lee HJ, Choi SY, Park JY, Ahn SY, et al. Proliferative glomerulopathy with unusual subendothelial

deposits of striated structure in multiple myeloma. Korean J Nephrol. 2010; 29(6),772–5.

13. Hara S, Tsukaguchi H, Oka T, Kusabe M, Mizui M, Joh K. Monoclonal immunoglobulin-associated proliferative glomerulonephritis characterized by organized deposits of striated ultra-substructures: a case report. Ultrastruct Pathol. 2017 Jul-Aug;41(4):301–7.

14. Gumber R, Cohen JB, Palmer MB, Kobrin SM, Vogl DT, Wasserstein AG, et al. A clone-directed approach may improve diagnosis and treatment of proliferative glomerulonephritis with monoclonal immunoglobulin deposits. Kidney Int. 2018 Jul;94(1):199–205.

15. Larsen CP, Messias NC, Walker PD, Fidler ME, Cornell LD, Hernandez LH, et al. Membranoproliferative glomerulonephritis with masked monotypic immunoglobulin deposits. Kidney Int. 2015 Oct;88(4):867–73.

16. Mii A, Shimizu A, Takada D, Tsuruoka S. Proliferative glomerulonephritis with unusual microlamellar organized deposits related to monoclonal immunoglobulin G3 (IgG3) kappa. CEN Case Rep. 2018 Nov; 7(2): 320–4.

Figure legends

Fig. 1. Light microscopic findings of the third allograft biopsy 3 months after transplantation. (a) The glomerulus showing mesangial hypercellularity and nodules (periodic acid-Schiff staining, 400×). (b) Double-contour glomerular basement membrane and mesangial interposition (Jones silver methenamine, 400×). (c, d) The glomerulus with a crescent (c) and endocapillary hypercellularity (d) (Jones silver methenamine, 400×).

Fig. 2. Immunohistochemistry of paraffin-embedded tissues digested with proteinase for the third allograft biopsy specimens 3 months after transplantation. Monoclonal immunoglobulin G, subclass 1, κ light chain deposits with peripheral and mesangial pattern. (400×).

Fig. 3. Electron microscopic findings of the second biopsy of the native kidney (A, B) and the third allograft biopsy 3 months after transplantation (C, D). (A) Electron-dense deposits accumulated in the subendothelial space (3,000×). (B) Higher magnification of deposits showing striated myofibril-like ultrastructure (20,000×). (C) Some electron-dense deposits (arrow) were observed in the subendothelial space in the allograft biopsy (3,000×). (D) Higher magnification of deposits in the allograft biopsy specimen, similar to those in the native kidney (15,000×). The width and distance of periodicity of these electron-dense bands were approximately 10–12 nm and 25–30 nm, respectively.